



Mobile phase effects in reversed-phase liquid chromatography: A comparison of acetonitrile/water and methanol/water solvents as studied by molecular simulation

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ABSTRACT

Molecular simulations of water/acetonitrile and water/methanol mobile phases in contact with a C₁₈ stationary phase were carried out to examine the molecular-level effects of mobile phase composition on structure and retention in reversed-phase liquid chromatography. The simulations indicate that increases in the fraction of organic modifier increase the amount of solvent penetration into the stationary phase and that this intercalated solvent increases chain alignment. This effect is slightly more apparent for acetonitrile containing solvents. The retention mechanism of alkane solutes showed contributions from both partitioning and adsorption. Despite changes in chain structure and solvation, the molecular mechanism of retention for alkane solutes was not affected by solvent composition. The mechanism of retention for alcohol solutes was primarily adsorption at the interface between the mobile and stationary phase, but there were also contributions from interactions with surface silanols. The interaction between the solute and surface silanols become very important at high concentrations of acetonitrile.

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1. Introduction

Reversed-phase liquid chromatography (RPLC) is among the most popular methods for the separation and analysis of chemical mixtures. Despite this popularity and decades of research, the complex interplay between solvent, stationary phase and solute that enacts a separation in RPLC is not fully understood. Retention in RPLC is driven by the distribution of solute molecules between the mobile phase (an aqueous/organic mixture) and the stationary phase (typically C₁₈ alkyl chains tethered to silica surface). However, the molecular-level events that drive this distribution, or the retention mechanism, have been a topic of study for over 30 years and the key details are still not settled [1–26]. For example, there are conflicting views as to whether adsorption at the stationary phase/mobile phase interface or full partitioning into the stationary phase is more important for solute retention and to what extent various chromatographic parameters, such as mobile phase composition and grafting density, affect this mechanism [14,18,21,26]. Even if partitioning is taken to be the dominant mechanism of retention, it is not clear if the process can be modeled accurately by

bulk liquid–liquid (e.g., oil–water) partitioning [14,23] or if partitioning into the tethered hydrocarbon chains of the RPLC stationary phase involves a different molecular mechanism [16,22]. Furthermore, it is debated whether the thermodynamic driving forces for solute retention (transfer from mobile to stationary phase) are primarily solvophobic [21] or lipophilic [14,23]. Here, solvophobic refers to the unfavorable interaction that an analyte molecule experiences with the polar mobile phase and lipophilic refers to favorable interaction with the nonpolar stationary phase.

The problem of pinpointing the retention mechanism in RPLC is further exacerbated by an incomplete understanding of the interaction between the mobile phase and the stationary phase. It is generally held that the organic component of the aqueous/organic mobile phase preferentially solvates the stationary phase. However, it is not fully resolved if this excess solvation occurs mainly through the formation of an organic layer atop the stationary phase [27,28] or if penetration of the organic modifier into the stationary phase is also important [29,30]. In the former case, retention could be affected by partitioning of the solutes into this organic layer, and in the latter case, solutes may compete with solvent molecules for space inside the stationary phase. In addition, changes in the level of solvation of the stationary phase with changing mobile phase composition may effect the conformation of the alkyl chains and alter their retentive properties.

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For a true understanding of structure and retention in RPLC, molecular-level information is needed. However, it is often very difficult to attain these molecular details through experiments alone. For this reason, molecular simulation, which can provide these details directly, has been employed by numerous groups and has become an increasingly popular means for studying RPLC [31–59]. A critical aspect of simulating RPLC is the ability of the simulation technique to reproduce experimental retention data. If the simulation is unable to accurately generate these data, then it is difficult to have confidence in the corresponding molecular details. Our recent studies have shown that molecular simulations using efficient sampling algorithms and accurate force fields can yield high precision retention data that are in quantitative agreement with experiment [52,53,55–59]. Although much useful and interesting data have come from the simulations carried out by other groups [31,32,34–47,49], a demonstrated ability to accurately and precisely model solute retention has been lacking in these studies.

In a continuing effort by us to systematically discern the molecular-level effects of various chromatographic parameters on structure and retention in RPLC, the influences of methanol concentration in the mobile phase [52], alkyl chain length [56], grafting density [54,55,59], polar-embedded groups [53,56], pressure [56], and pore shape [56] have been examined. In the present work the effect of two organic modifiers at various concentrations is examined by carrying out simulations for a medium-coverage dimethyl octadecylsilane stationary phase in contact with various water/acetonitrile and water/methanol mixtures.

The effect of organic modifier concentration is an important topic because selectivity in RPLC is most often optimized by adjusting the composition of the mobile phase. In addition to the concentration, the identity of the organic modifier is also important. It has been suggested that the mechanism of retention can be altered when different organic modifiers are used. For example, the retention mechanism is thought to be more adsorption-like for water/acetonitrile and more partition-like for water/methanol mixtures [25]. Furthermore, the thermodynamics of the retention process are different depending on whether water/methanol or water/acetonitrile is used [23,60–63]. It is thought this may result from acetonitrile's greater affinity to aggregate around the solutes as compared to methanol [60–62] or that acetonitrile penetrates the stationary phase to a larger extent than methanol [63].

2. Simulation details

The simulation methodology used in this work closely follows our previous work [52–57]. Thus, only the salient features are described in this section and the reader is referred to [57] for a very detailed description. To examine the effects of mobile phase composition in RPLC we make use of coupled–decoupled configurational-bias Monte Carlo simulations (CBMC) [64–68] in the isobaric–isothermal version of the Gibbs ensemble [69,70]. The simulations are carried out at a temperature of 323 K and a pressure of 1 atm and make use of three separate simulation boxes that are in thermodynamic contact but do not share an explicit interface (a graphical representation of the three-box set-up can be found in [54]). The first simulation box corresponds to a planar slit pore with two substrates, (1 1 1) surfaces of β -cristobalite separated by about 70 Å along the z-direction, to which dimethyl octadecylsilane chains are grafted at a density of 2.9 $\mu\text{mol}/\text{m}^2$ resulting in a residual silanol density of 4.8 $\mu\text{mol}/\text{m}^2$. The remainder of this pore is filled by mobile phase solvent. The second box contains a bulk mobile phase reservoir and the third box a helium vapor phase. These boxes are cubic and their volumes are allowed to fluctuate in response to the external pressure. In these Gibbs ensemble simulations, solvent and solute molecules are allowed to move between

the three boxes, thereby ensuring that the chemical potentials of solvent species and analyte compounds are equal in the stationary phase box, the bulk solvent reservoir, and the vapor phase.

The vapor box present in these simulation serves as an ideal gas reference state, which allows one to decompose the free energy of retention into mobile and stationary phase components (ΔG_{mob} and ΔG_{stat} , respectively) [57,58].

Seven different aqueous/organic mobile phase compositions are compared: pure water, 33% molfraction acetonitrile, 67% molfraction acetonitrile, pure acetonitrile, 33% molfraction methanol, 67% molfraction methanol, and pure methanol (hereafter referred to as systems WAT, 33A, 67A, ACN, 33M, 67M, and MET, respectively). The data for systems WAT, 33M, 67M, and MET are taken from [51] and [52]. Each system contained from 768 to 1200 solvent molecules and 16 solutes (two each of C₁ to C₄ normal alkanes and alcohols).

To describe molecular interactions in the model RPLC system, the TraPPE force field [67,71–74] was used for alkanes, alcohols, acetonitrile, and helium. Water was described by the TIP4P model [75] and silica by a rigid zeolite potential [76–78]. Surface silanols were given bending and torsional degrees of freedom and had charges assigned based on the TraPPE alcohol model (−0.739e for oxygen, +0.435e for hydrogen) [72]. Lennard-Jones interactions were truncated at a distance of 10 Å and Coulombic interactions were treated with the Ewald summation technique [79] using a direct space cutoff of 10 Å and a convergence parameter of $\kappa = 0.28$. The number of reciprocal space vectors used in each direction of a box was equal to the next integer greater than $\kappa \times L_\alpha$, where L_α is the box length in that direction. It should be noted here that structural features and solvation thermodynamics can be very sensitive to the details of the molecular models (i.e., the underlying force fields). For example, relatively small changes in the partial charges and Lennard-Jones parameters used for acetonitrile were found to significantly alter the degree of micro-heterogeneity in water/acetonitrile mixtures [80]. Similarly, small changes in only the Lennard-Jones parameters of the alkyl tail were found responsible for large changes in water solubility, structure, and solute partitioning for octanol–water liquid–liquid equilibria [81,82]. Thus, with respect to computational investigations of retention mechanisms, it is of utmost importance to validate predicted retention data against experimental values.

For each solvent composition studied, four independent simulations were carried out. Each simulation was equilibrated for 2×10^5 Monte Carlo (MC) cycles (one MC cycle corresponds to N MC moves, where N is the total number of molecules in the system). Thereafter, the simulations proceeded with an additional 2×10^5 MC cycles during which averages were collected. Statistical uncertainties in all reported quantities were estimated from the standard error of the mean of the averages from the four independent simulations.

3. Results and discussion

Snapshots from the simulations at each solvent composition are shown in Fig. 1. Although each of these snapshots represents only a single configuration of the millions generated during the simulation, they already demonstrate some of the distinct differences between the seven solvent systems. As the fraction of organic modifier is increased, there is significantly more penetration of solvent into the stationary phase. Near the silica surface, most of this solvent is water. However, throughout the remainder of the stationary phase the majority of the sorbed solvent appears to be the organic modifier. In comparing systems with the same fraction of organic modifier, more solvent penetration is observed for the acetonitrile containing systems. Also appearing enriched in organic component of the solvent is the interfacial region between the stationary and

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